MMAA gene

methylmalonic aciduria (cobalamin deficiency) cblA type

Normal Function

The *MMAA* gene provides instructions for making a protein that is involved in the formation of a compound called adenosylcobalamin (AdoCbl). AdoCbl, which is derived from vitamin B12 (also called cobalamin), is necessary for the normal function of an enzyme known as methylmalonyl CoA mutase. This enzyme helps break down certain proteins, fats (lipids), and cholesterol.

Research indicates that the MMAA protein may play a role in one of the last steps in AdoCbl formation, the transport of vitamin B12 into mitochondria (specialized structures inside cells that serve as energy-producing centers). Additional chemical reactions then convert vitamin B12 into AdoCbl. Other studies suggest that the MMAA protein may help stabilize methylmalonyl CoA mutase and protect the enzyme from being turned off (inactivated).

Health Conditions Related to Genetic Changes

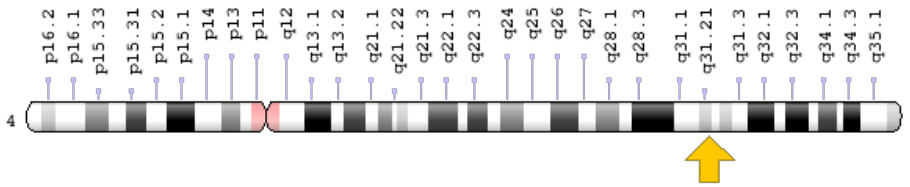
methylmalonic acidemia

More than 25 mutations in the *MMAA* gene have been found to cause methylmalonic acidemia, a condition characterized by feeding difficulties, developmental delay, and long term health problems. Some of these mutations add, delete, or duplicate a small amount of genetic material in the gene. Other mutations change a single protein building block (amino acid) used to make the MMAA protein. These mutations can lead to the production of an unstable MMAA protein or an abnormally small, nonfunctional version of the protein. It is unclear how the abnormal MMAA protein leads to the serious medical problems associated with methylmalonic acidemia. Studies suggest that without the activity of this protein, AdoCbl may not be made properly. A lack of AdoCbl impairs the function of methylmalonyl CoA mutase, which results in the incomplete break down of certain proteins and lipids. This defect allows toxic compounds to build up in the body's organs and tissues. Research suggests that a lack of AdoCbl leading to impaired methylmalonyl CoA mutase function causes the signs and symptoms of methylmalonic acidemia.

Chromosomal Location

Cytogenetic Location: 4q31.21, which is the long (q) arm of chromosome 4 at position 31.21

Molecular Location: base pairs 145,619,388 to 145,660,035 on chromosome 4 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- cblA
- methylmalonic aciduria (cobalamin deficiency) type A
- methylmalonic aciduria type A
- MMAA_HUMAN

Additional Information & Resources

Educational Resources

- Basic Neurochemistry (sixth edition, 1999): Methylmalonic aciduria may be secondary to defects of cobalamin metabolism
  https://www.ncbi.nlm.nih.gov/books/NBK27933/#A3118

GeneReviews

- Isolated Methylmalonic Acidemia
  https://www.ncbi.nlm.nih.gov/books/NBK1231

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28MMAA%5BTIAB%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D

OMIM

- MMAA GENE
  http://omim.org/entry/607481

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_MMAA.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=MMAA%5Bgene%5D
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=18871
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/166785
- UniProt
  http://www.uniprot.org/uniprot/Q8IVH4

Sources for This Summary

- Chandler RJ, Venditti CP. Genetic and genomic systems to study methylmalonic acidemia. Mol Genet Metab. 2005 Sep-Oct;86(1-2):34-43. Epub 2005 Sep 22. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16182581
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2657357/
- Dobson CM, Wai T, Leclerc D, Wilson A, Wu X, Doré C, Hudson T, Rosenblatt DS, Gravel RA. Identification of the gene responsible for the cblA complementation group of vitamin B12-responsive methylmalonic acidemia based on analysis of prokaryotic gene arrangements. Proc Natl Acad Sci U S A. 2002 Nov 26;99(24):15554-9. Epub 2002 Nov 15.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12438653
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC137755/
- Froese DS, Kochan G, Muniz JR, Wu X, Gileadi C, Ugochukwu E, Krysztofinska E, Gravel RA, Oppermann U, Yue WW. Structures of the human GTPase MMAA and vitamin B12-dependent methylmalonyl-CoA mutase and insight into their complex formation. J Biol Chem. 2010 Dec 3; 285(49):38204-13. doi: 10.1074/jbc.M110.177717. Epub 2010 Sep 28.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20876572
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2992254/
- GeneReview: Isolated Methylmalonic Acidemia
  https://www.ncbi.nlm.nih.gov/books/NBK1231
- Hörster F, Baumgartner MR, Viardot C, Suormala T, Burgard P, Fowler B, Hoffmann GF, Garbade SF, Kölker S, Baumgartner ER. Long-term outcome in methylmalonic acidurias is influenced by the underlying defect (mut0, mut-, cblA, cblB). Pediatr Res. 2007 Aug;62(2):225-30.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17597648

- Korotkova N, Lidstrom ME. MeaB is a component of the methylmalonyl-CoA mutase complex required for protection of the enzyme from inactivation. J Biol Chem. 2004 Apr 2;279(14):13652-8. Epub 2004 Jan 20.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/14734568
- Lerner-Ellis JP, Dobson CM, Wai T, Watkins D, Tirone JC, Leclerc D, Doré C, Lepage P, Gravel RA, Rosenblatt DS. Mutations in the MMAA gene in patients with the cblA disorder of vitamin B12 metabolism. Hum Mutat. 2004 Dec;24(6):509-16. Erratum in: Hum Mutat. 2005 Mar;25(3):317.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15523652
- Yang X, Sakamoto O, Matsubara Y, Kure S, Suzuki Y, Aoki Y, Suzuki Y, Sakura N, Takayanagi M, Iinuma K, Ohura T. Mutation analysis of the MMAA and MMAB genes in Japanese patients with vitamin B(12)-responsive methylmalonic acidemia: identification of a prevalent MMAA mutation. Mol Genet Metab. 2004 Aug;82(4):329-33.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15308131

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